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Gene Therapy

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13. ABSTRACT (Maximum 200 Words) <p>Background: Combination of the cytotoxic viral thymidine kinase (tk) and the prodrug, acyclovir (ACV) has been reported to inhibit the growth of the C4-2 tumor, a subline of LNCaP. However, it remains unsolved to non-invasively detect the in vivo distribution, expression and persistence of the toxic gene as well as to evaluate the therapeutic effect. In this project, we will develop a nuclear gene imaging approach to assist the cytotoxic gene therapy study for prostate cancer.</p> <p>Objective/Hypothesis: The distribution, expression, and persistence of the prostate specific Ad-PSA-tk in the C4-2 tumor xenograft model will be non-invasively and repeatedly determined in vivo by tracing the I-123 labeled TK substrates with a SPECT imaging modality.</p> <p>Specific Aim of the first year: To synthesize a radiolabeled TK substrate for TK detection using a small animal gamma detector. In the original plan, we proposed to develop a novel synthetic method of [I-123]IVFRU with high specificity. However, after careful literature study, we decide to modify our target molecule labeled with Tc-99m because of its superior physical characteristics (T1/2 = 6h, 140 keV), high specific activity (5 x 105 Ci/mmol), and straightforward production from a Mo-99/Tc-99m generator.</p> <p>Progress and outcome: Although the grant was awarded on March of 2002, due to the hiring process of a postdoctoral fellow the research was started on 10 Sep 2002. Currently, we are in the process of synthesizing 2'-Deoxy-2'-fluoro-5-[3-oxo[N,N-bis(2-mercaptoethyl)ethylenediaminato][Tc-99m] technetium(V)-1(E)-propeny]uridine, a proposed TK substrate.</p>				
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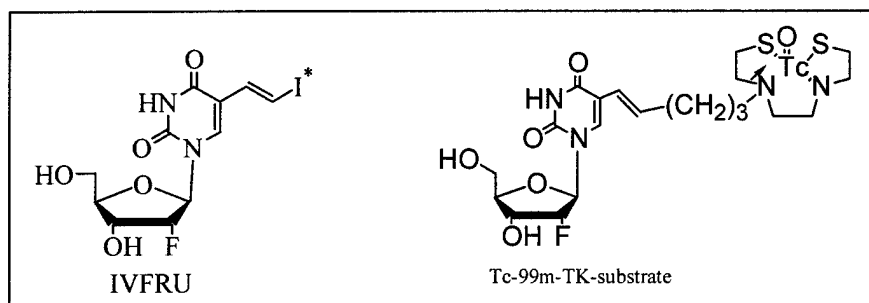
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Introduction

The objective of this project is to develop a noninvasive imaging assay using single photon emission computed tomography (SPECT) for assessment of gene therapeutic efficacy and diagnosis of metastasis of prostate cancer.

Currently, nuclear imaging technology has demonstrated the greatest potential to non-invasively image gene activity in animals and humans due to its high sensitivity. By replacing the acyclovir (ACV) with a radioactive analogue, it is possible to non-invasively and repeatedly monitor the *in vivo* distribution of the transduced tk construct. It may assist in determining the optimal timing for ACV administration, confirming the cytotoxic sites, and assessing the therapeutic efficacy. Further refinement of this technology could also provide a non-invasive approach to identify any metastasis sites in a clinical setting.



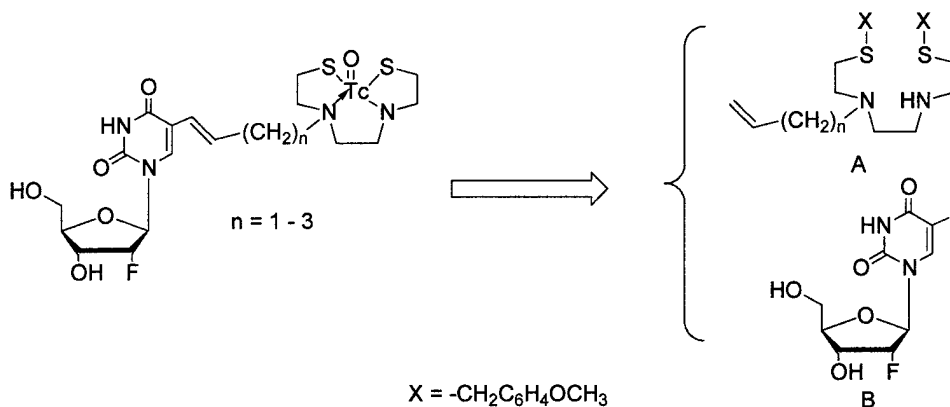
In the first year of the plan, we proposed to synthesize a novel thymidine kinase (TK) substrate, I-123 labeled 1-(2-deoxy-2-fluoro- β -D-ribofuranosyl)-

5(E)-(2-iodovinyl)uracil (IVFRU).

With the recent progress of Tc-99m chemistry, Tc-99m labeled radiopharmaceuticals, such as TRODAT, have demonstrated to be membrane permeable. This raises our interest to synthesize a Tc-99m labeled TK substrate for gene imaging, because of the nearly optimal nuclear properties of Tc-99m, as well as its convenient and low cost production by means of commercial generator columns. As a result, we modified our plan by switching the target molecule, [I-123]IVFRU with 2'-Deoxy-2' fluoro-5-{3-oxo[N,N-bis(2-mercaptoethyl)ethylenediamato][Tc-99m] technetium(V)-1(E)-propenyl}uridine.

Body

The target molecule will be convergently synthesized from compounds A and B.

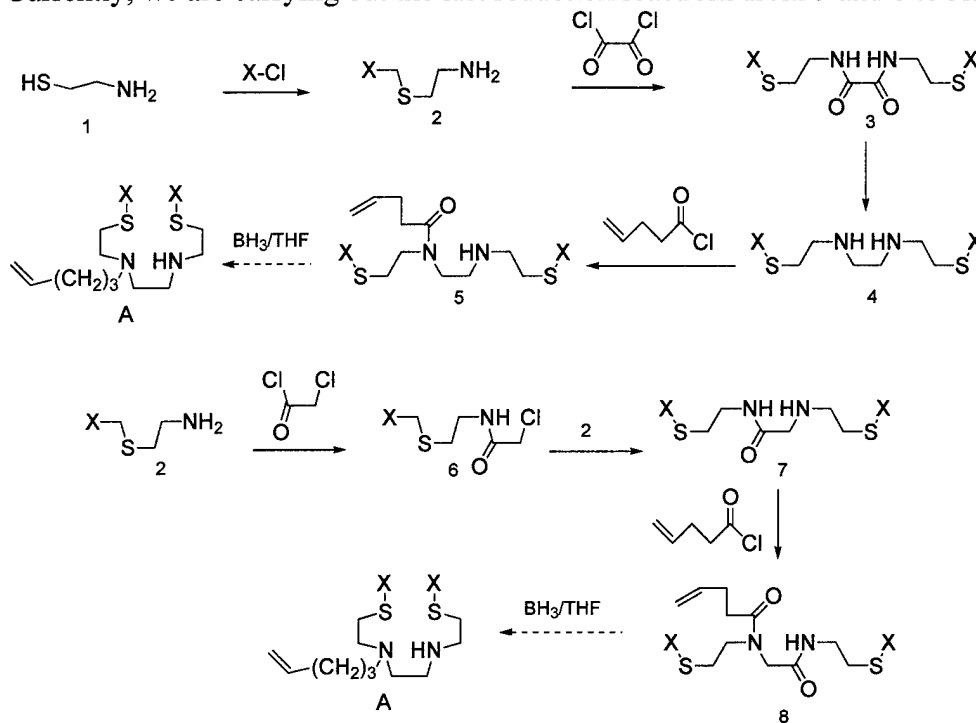


Scheme 1

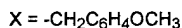
Synthetic progress

Due to the hiring process of a postdoctoral fellow the research was started on 10 Sep 2002. The progress of the project in the first 6 months is listed below.

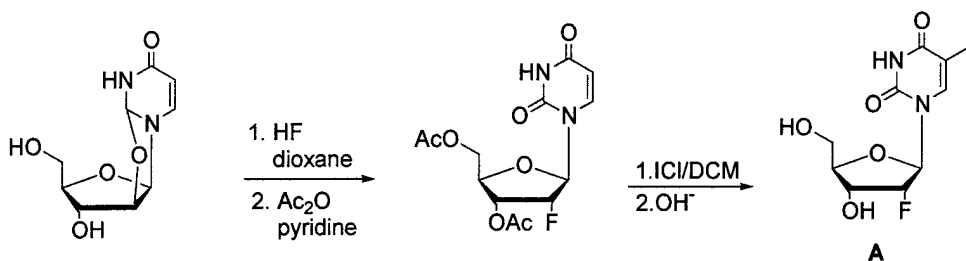
Compound A. Two synthetic routes to chelator A have been explored (Scheme 2). Currently, we are carrying out the last reduction reactions from 5 and 8 to A.



Scheme 2



Compound B. The compound B was synthesized as described in Scheme 3.



Scheme 3

Key Research Accomplishments:

The project was started on Sept. 10 of 2002 and we are in the process to synthesize the Tc-99m labeled TK substrate.

Reportable Outcomes:

Please see the section of synthetic progress in above section.

Conclusions:

We will obtain the Tc-99m labeled TK substrate by Sept. of 2003, the end of the first year of the project.